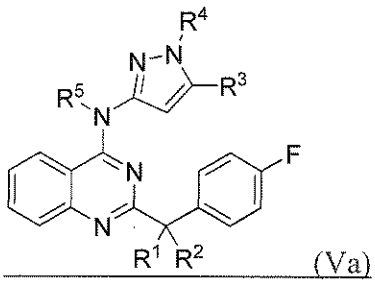
*Transplantation* (2005) 79(7):791-801 and Milici *et al.*, *Arthritis Research* (2008) 10(R14):1-9

**[0008]** Given the multitude of diseases attributed to the dysregulation of JAK signaling, many small molecule inhibitors of JAK are currently being developed. Examples of compounds in preclinical development include TG101209 (TargeGen), examples are compounds being investigated in clinical studies include INCB018424 (Incyte), XL019 (Exelixis) and TG101348 (TargeGen). *See,* Pardanani *et al. Leukemia* 2007, 21:1658-1668; and Pardanai, A. *Leukemia* 2008 22:23-20.

**[0009]** There is, however, an ever-existing need to provide novel classes of compounds that are useful as inhibtors of enzymes in the JAK signaling pathway.

**SUMMARY**

**[0009a]** In a first aspect, the present invention refers to a A compound having formula (Va)




(Va)

or a pharmaceutically acceptable salt thereof, where

$R^1$ and $R^2$ are selected from (i), (ii), and (iii) as follows:

(i) $R^1$ and $R^2$ together form =O;

(ii) $R^1$ is hydrogen or halo, and $R^2$ is halo; and

(iii) $R^1$ is hydroxyl, $C_{1-6}$alkoxy, amino, -NHCH(O) or $C_{1-6}$alkoxycarbonylamino, and $R^2$ is hydrogen or $C_{1-6}$alkyl;

$R^3$ is hydrogen or $C_{1-6}$alkyl;

$R^4$ is hydrogen; and

$R^5$ is hydrogen.

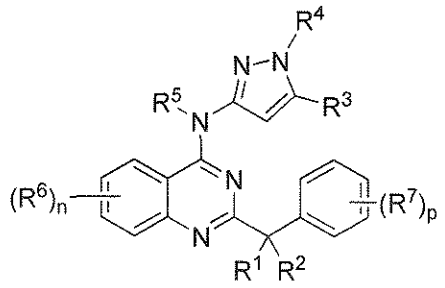
**[0009b]** In a second aspect, the present invention refers to the compound (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(2-methoxyphenyl) methanone or 3-(2-((4-fluorophenyl)(hydroxy)methyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile.

**[0009c]** In a third aspect, the present invention refers to a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier or excipient.

**[0009d]** In a fourth aspect, the present invention refers to the use of a therapeutically effective amount of a compound of the present invention in the manufacture of a medicament for treatment of cancer, or myeloproliferative disorder, or inflammation or autoimmune disease.

**[0009e]** In a fifth aspect, the present invention refers to the compound of the present invention for use in treatment of cancer, or myeloproliferative disorder, or inflammation or autoimmune disease.

**[0010]** Disclosed~~Provided~~ herein are compounds of formula (I)



(I)

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

$R^1$ and $R^2$ are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) $R^1$ and $R^2$ together form =O, =S, $=NR^9$ or $=CR^{10}R^{11}$;

(ii) $R^1$ and $R^2$ are both $-OR^8$, or $R^1$ and $R^2$, together with the carbon atom to which they are attached, form dioxacycloalkyl;

(iii) $R^1$ is hydrogen or halo; and $R^2$ is halo;

(iv) $R^1$ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl or aryl is optionally substituted with one or more, in one embodiment, one to four, in one example~~embodiment~~, one to three, in one example~~embodiment~~, one, two or three, substitutents selected from halo, cyano, alkyl, $-R^xOR^w$, $-R^xS(O)_qR^v$, $-R^xNR^yR^z$ and $-C(O)OR^w$; and $R^2$ is hydrogen, halo or $-OR^8$; and

(v) $R^1$ is halo, deutero, $-OR^{12}$, $-NR^{13}R^{14}$, or $-S(O)_qR^{15}$; and $R^2$ is hydrogen, deutero, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl or aryl is optionally substituted with one or more, in one example~~embodiment~~, one to four, in one embodiment, one to three, in one example~~embodiment~~, one,

two or three, substitutents selected from halo, cyano, alkyl, $-R^xOR^w$, $-R^xS(O)_qR^v$ and $-R^xNR^yR^z$;

$R^3$ is hydrogen, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

$R^4$ and $R^5$ are each independently hydrogen or alkyl;

each $R^6$ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, $-R^xOR^{18}$, $-R^xNR^{19}R^{20}$, and $-R^xS(O)_qR^v$;

each $R^7$ is independently halo, alkyl, haloalkyl or $-R^xOR^w$;

$R^8$ is alkyl, alkenyl or alkynyl;

$R^9$ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

$R^{10}$ is hydrogen or alkyl;

$R^{11}$ is hydrogen, alkyl, haloalkyl or $-C(O)OR^8$;

$R^{12}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)R^v$, $-C(O)OR^w$ and $-C(O)NR^yR^z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one example~~embodiment~~, one to four, in one example~~embodiment~~, one to three, in one example~~embodiment~~, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R^{13}$ and $R^{14}$ are selected as follows:

(i) $R^{13}$ is hydrogen or alkyl; and $R^{14}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, $-C(O)R^v$, $-C(O)OR^w$, $-C(O)NR^yR^z$ and $-S(O)_qR^v$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl are each optionally substituted with one or more, in one example~~embodiment~~, one to four, in one example~~embodiment~~, one to three, in one example~~embodiment~~, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) $R^{13}$ and $R^{14}$, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one example~~embodiment~~, one to four, in one example~~embodiment~~, one to three,

in one example~~embodiment~~, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo;

$R^{15}$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)NR^yR^z$ or $-NR^yR^z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl are each optionally substituted with one or more, in one example~~embodiment~~, one to four, in one example~~embodiment~~, one to three, in one example~~embodiment~~, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R^{18}$ is hydrogen, alkyl, haloalkyl, hydroxy$C_{2-6}$alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein $R^{18}$ is optionally substituted with 1 to 3 groups $Q^1$, each $Q^1$ independently selected from alkyl, hydroxyl, halo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

$R^{19}$ and $R^{20}$ are selected as follows:

(i) $R^{19}$ and $R^{20}$ are each independently hydrogen or alkyl; or

(ii) $R^{19}$ and $R^{20}$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

each $R^x$ is independently alkylene or a direct bond;

$R^v$ is hydrogen, alkyl, alkenyl or alkynyl;

$R^w$ is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

$R^y$ and $R^z$ are selected as follows:

(i) $R^y$ and $R^z$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl;

(ii) $R^y$ and $R^z$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

n is 0-4;

p is 0-5; and

each q is independently 0, 1 or 2.

**[0011]** In certain example~~embodiments~~, the compounds have activity as JAK kinase, including JAK2 kinase, modulators. The compounds are useful in medical treatments, pharmaceutical compositions and methods for modulating the activity of JAK kinase, including wildtype and/or mutated forms of JAK kinase. In certain example~~embodiments~~, the compounds provided herein have activity as JAK2 kinase modulators. In certain example~~embodiments~~, the compounds are inhibitors of JAK kinase, including JAK2 kinase. In certain example~~embodiments~~, the compounds are inhibitors of JAK kinase, including JAK2 and TYK2 kinases.

**[0012]** In one example~~embodiment~~, the compounds for use in the compositions and methods disclosed~~provided~~ herein are compounds of formula (I).

**[0013]** In one example~~embodiment~~, the compound disclosed~~provided~~ herein is a compound of formula (I). In one example~~embodiment~~, the compound provided herein is a pharmaceutically acceptable salt of the compound of formula (I). In one example~~embodiment~~, the compound provided herein is a solvate of the compound of formula (I). In one example~~embodiment~~, the compound provided herein is a hydrate of compound of formula (I).

**[0014]** Also disclosed~~provided~~ are pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, solvates and hydrates thereof, and optionally comprising at least one pharmaceutical carrier.

**[0015]** Such pharmaceutical compositions deliver amounts effective for the treatment, prevention, or amelioration of diseases or disorders that include without limitation, myeloproliferative disorders such as polycythemia vera (PCV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML), systemic mastocytosis (SM) and idiopathic myelofibrosis (IMF); leukemia such as myeloid leukemia including chronic myeloid leukemia (CML), imatinib-resistant forms of CML, acute myeloid leukemia (AML), and a subtype of AML, acute megakaryoblastic leukemia (AMKL); lymphoproliferative diseases such as myeloma; cancer such as cancer of the head and neck, prostate cancer, breast cancer, ovarian cancer, melanoma, lung cancers, brain

tumors, pancreatic cancer and renal cancer; and inflammatory diseases or disorders related to immune dysfunction, immunodeficiency, immunomodulation, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosis (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma chronic obstructive pulmonary disease (COPD) and dry eye syndrome (or keratoconjunctivitis sicca (KCS)). In one example~~embodiment~~, such diseases or disorders are modulated or otherwise affected by the JAK kinases, including JAK2, JAK3 or TYK2.

**[0016]** Also disclosed~~provided~~ herein are combination therapies using one or more compounds or compositions provided herein, or pharmaceutically acceptable salts, solvates or hydrates thereof, in combination with other pharmaceutically active agents for the treatment of the diseases and disorders described herein.

**[0017]** In one example~~embodiment~~, such additional pharmaceutical agents include one or more chemotherapeutic agents, anti-proliferative agents, anti-inflammatory agents, immunomodulatory agents or immunosuppressive agents.

**[0018]** The compounds or compositions disclosed~~provided~~ herein, or pharmaceutically acceptable salts, solvates or hydrates thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound disclosed~~provided~~ herein and one or more of the above agents are also disclosed~~provided~~.

**[0019]** In certain example~~embodiments~~, disclosed~~provided~~ herein are methods of treating, preventing or ameliorating a disease or disorder that is modulated or otherwise affected by JAK kinases, including JAK2 kinase such as wild type and/or mutant JAK2 kinase, or one or more symptoms or causes thereof. In another example~~embodiment~~, disclosed~~provided~~ herein are methods of treating, preventing or ameliorating a disease or disorder by modulating the JAK2 kinase selectively over JAK3 kinase. In yet another example~~embodiment~~, disclosed~~provided~~ herein are methods of treating, preventing or ameliorating a disease or disorder by modulating the JAK3 kinase selectively over JAK2 kinase. In another example~~embodiment~~, disclosed~~provided~~ herein are methods of treating, preventing or amerliorating a disease or disorder by modulating both JAK2 and JAK3. In one

exampleembodiment, disclosedprovided are methods for treatment of cancer, including blood borne and solid tumors.

[0020] In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application are administered to an individual exhibiting the symptoms of the disease or disorder to be treated. The amounts are effective to ameliorate or eliminate one or more symptoms of the disease or disorder.

[0021] These and other aspects of the subject matter described herein will become evident upon reference to the following detailed description.

## BRIEF DESCRIPTION OF DRAWINGS

[0022] Figure 1 provides *in vivo* data to demonstrate dose responsive effects of a compound of Formula I in rat Type II Collagen-Induced Arthritis (CIA) model.

[0023] Figure 2 provides effects of administration of various doses of a compound of Formula I and control on body weight in the rat Type II Collagen-Induced Arthritis (CIA) model.

[0024] Figure 3 provides a Kaplan Meier survival analysis for an Ambit internal compound, TGEN101348 and control in the mouse TELJAK mouse model.

[0025] Figure 4 provides a Kaplan Meier survival analysis for an Ambit internal compound, a compound of Formula I and control in the mouse TELJAK mouse model.

[0026] Figure 5 provides a Kaplan Meier survival analysis for an Ambit internal compound, a compound of Formula I and control in the mouse HELV617F liquid tumor model.

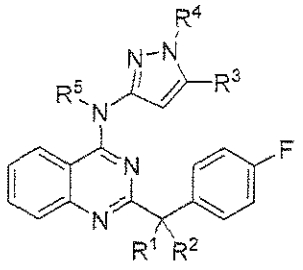
[0027] Figure 6 provides a Kaplan Meier survival analysis for an Ambit internal compound, TGEN101348 and control in the mouse HELV617F liquid tumor model.

## DETAILED DESCRIPTION

[0028] Provided herein are compounds of formula (I) that have activity as JAK kinase, including JAK2 kinase, modulators. Further provided are methods of treating, preventing or ameliorating diseases that are modulated by JAK kinases, including JAK2 kinase, and pharmaceutical compositions and dosage forms useful for such methods. The methods and compositions are described in detail in the sections below.

**What is claimed is:**

1. A compound having formula (Va)



(Va)

or a pharmaceutically acceptable salt thereof, where

$R^1$ and $R^2$ are selected from (i), (ii), and (iii) as follows:

(i) $R^1$ and $R^2$ together form =O;

(ii) $R^1$ is hydrogen or halo, and $R^2$ is halo; and

(iii) $R^1$ is hydroxyl, $C_{1-6}$alkoxy, amino, -NHCH(O) or $C_{1-6}$alkoxycarbonylamino, and $R^2$ is hydrogen or $C_{1-6}$alkyl;

$R^3$ is hydrogen or $C_{1-6}$alkyl;

$R^4$ is hydrogen; and

$R^5$ is hydrogen.

2. The compound of claim 1, wherein $R^1$ and $R^2$ together form =O.

3. The compound of claim 1 or 2, wherein $R^1$ is hydrogen or fluoro, and $R^2$ is fluoro.

4. The compound of claim 1 or 2, wherein $R^1$ is hydroxyl, methoxy, amino or methoxycarbonylamino, and $R^2$ is hydrogen.

5. The compound of claim 1 selected from:

(4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone;

(4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanone;

(4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(2-methoxyphenyl) methanone;

(4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol;

2-(fluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine;

(4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanol;

2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine;

2-(amino(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine;

3-(2-((4-fluorophenyl)(hydroxy)methyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile;
{(4-fluoro-phenyl)-[4-(5-methyl-1H-pyrazol-3-ylamino)-quinazolin-2-yl]-methyl}-carbamic acid methyl ester;
N-((4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methyl)formamide; and
(4-(5-ethyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol.

6. A pharmaceutical composition comprising a compound of any of claims 1-5 and a pharmaceutically acceptable carrier or excipient.

7. Use of a therapeutically effective amount of a compound of any of claims 1-5 in the manufacture of a medicament for treatment of a JAK modulated disease.

8. Use of a therapeutically effective amount of a compound of any of claims 1-5 in the manufacture of a medicament for treatment of a JAK2 modulated disease.

9. The use of claim 8, wherein JAK2 is wild type or mutant JAK2.

10. The use of claim 7, wherein the disease is cancer, myeloproliferative disorder, inflammation or autoimmune disease.

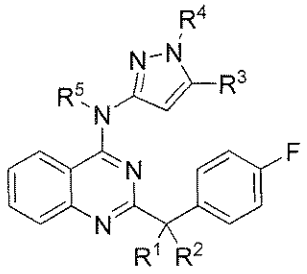
11. The use of claim 7 or 8, wherein the medicament further comprises a second pharmaceutical agent selected from anti-proliferative agent, anti-inflammatory agent, and immunomodulatory agent.

12. The compound of any of claims 1-5 for use in treatment of a JAK modulated disease.

13. Use of the compound of any of claims 1-5 for preparation of a medicament for treating a JAK modulated disease.

**What is claimed is:**

1. A compound having formula (Va)



(Va)

or a pharmaceutically acceptable salt thereof, where

$R^1$ and $R^2$ are selected from (i), (ii), and (iii) as follows:

(i) $R^1$ and $R^2$ together form =O;

(ii) $R^1$ is hydrogen or halo, and $R^2$ is halo; and

(iii) $R^1$ is hydroxyl, $C_{1-6}$alkoxy, amino, -NHCH(O) or $C_{1-6}$alkoxycarbonylamino, and $R^2$ is hydrogen or $C_{1-6}$alkyl;

$R^3$ is hydrogen or $C_{1-6}$alkyl;

$R^4$ is hydrogen; and

$R^5$ is hydrogen.

2. The compound of claim 1, wherein $R^1$ and $R^2$ together form =O.

3. The compound of claim 1 or 2, wherein $R^1$ is hydrogen or fluoro, and $R^2$ is fluoro.

4. The compound of claim 1 or 2, wherein $R^1$ is hydroxyl, methoxy, amino or methoxycarbonylamino, and $R^2$ is hydrogen.

5. The compound of claim 1 selected from:

(4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone;

(4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanone;

(4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol;

2-(fluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine;

(4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanol;

2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine;

2-(amino(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine;

{(4-fluoro-phenyl)-[4-(5-methyl-1H-pyrazol-3-ylamino)-quinazolin-2-yl]-methyl}-carbamic acid methyl ester;

N-((4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methyl)formamide; and

(4-(5-ethyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol.

6. The compound (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(2-methoxyphenyl) methanone or 3-(2-((4-fluorophenyl)(hydroxy)methyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile.

7. A pharmaceutical composition comprising a compound of any of claims 1-6 and a pharmaceutically acceptable carrier or excipient.

8. Use of a therapeutically effective amount of a compound of any of claims 1-6 in the manufacture of a medicament for treatment of cancer, or myeloproliferative disorder, or inflammation or autoimmune disease.

9. The use of claim 8, wherein the medicament further comprises a second pharmaceutical agent selected from anti-proliferative agent, anti-inflammatory agent, and immunomodulatory agent.

10. The compound of any of claims 1-6 for use in treatment of cancer, or myeloproliferative disorder, or inflammation or autoimmune disease.